

**Amendments to the Drawings:**

Two sheets of Substitute Drawings are attached and each are clearly marked "Replacement Sheet" accordingly. The attached sheets of drawings include changes to Figures 4 and 5. These sheets replace the Replacement Sheets previously filed on July 25, 2005, which were filed in error.

The description of the changes to Figures 4 and 5 that were submitted in the Preliminary Amendment dated July 25, 2005 clearly do not correspond to the drawings that were filed concurrently. For example, the Preliminary Amendment states changes to Figure 4 at page 2 as follows:

"...each of the pressures (P) relating to those elements have been assigned new Reference Numbers **21, 20, 22** and **23**, respectively." The Figure 4 drawing submitted therewith, however, shows no such Reference Numbers.

Moreover, the Preliminary Amendment states changes to Figure 5 at page 2 as follows:

"...new Reference Numbers **21, 20, 22** and **23** have been added..." and "...inert gas valve **16** has been re-named **16A**...". The Figure 5 drawing submitted therewith, however, shows no such Reference Numbers.

While the description of the changes to the drawings submitted in the Preliminary Amendment dated July 25, 2005 were correct, the drawings submitted therewith were not. The sheets of drawings submitted herewith clearly correspond to the description of record.

### **Pending Claims**

After entry of the foregoing amendment, the status of the claims is as follows:

Pending: 1-10, 12-35, 49, 51-53, 55-72, 74-81 and 84-89

Canceled: 11, 36-48, 50, 54, 73 and 82-83

Currently amended: None

Applicants respectfully request cancellation of claims 82 and 83 without prejudice. Applicants do not concede to the correctness of the Examiner's rejection in the Office Action dated October 17, 2005, however these claims have been canceled in order to narrow the outstanding issues and to assist in expediting and concluding the prosecution of the remaining claims. Applicants reserve the right to pursue these claims in a continuation or divisional application.

### **Rejections Under 35 U.S.C. §102**

Claims 82 and 83 stand rejected under 35 U.S.C. §102(b) as being anticipated by Kim *et al.* (Cancer Treatment Reports, 1987), or Assil *et al.* (Arch. Ophthalmol., 1987), or Bonetti *et al.* (Cancer Chemother. Pharmacol., 1994), or Kim *et al.* (5,723,147) or Sankaram *et al.* (5,766,627). This rejection is moot in view of the cancellation of the claims.

### **Rejections Under 35 U.S.C. §103**

Claims 1-10, 12-35, 49 and 51-53, 55-72 and 74-89 stand rejected under 35 U.S.C. §103 as being unpatentable over Kim *et al.* (Cancer Treatment Reports, 1987), or Assil *et al.* (Arch. Ophthalmol., 1987), or Bonetti *et al.* (Cancer Chemother. Pharmacol., 1994), or Kim *et al.* (5,723,147), or Sankaram *et al.* (5,766,627), in view of Lenke *et al.* (5,948,441), optionally in further combination with Bosworth *et al.* (5,407,660).

The Examiner has stated that the cited references all teach basically the same process of preparation of multivesicular liposomes, but that the references lack teachings of cross-flow filtration and sterilization. Applicants respectfully disagree with this basis of rejection for the following reasons.

Claim 1 does not recite a sterilization step. Claim 1, however, does recite a sparging step comprising at least two phases conducted at different gas flow rates. None of the cited references disclose or suggest such a step for the production of multivesicular liposomes. The Examiner has suggested that any person having ordinary skill in the art would know to use a multi-step process of solvent removal employing different gas flow rates. As evidence of this, the Examiner cites Bosworth *et al.* (hereinafter “the ‘660 reference”).

The ‘660 reference discloses a process for making paramagnetic liposome preparations for use in NMR procedures. The ‘660 reference does not teach or suggest preparation of multivesicular liposomes, which differ greatly from other liposomes in the manner in which they are produced, as well as in the inherent properties that they possess. The Examiner specifically points to Example 2 of the ‘660 reference. In that method for producing the paramagnetic liposome preparation, the solvent removal step was conducted by vacuum, not by sparging. The vacuum process was conducted prior to liposome formation. Methods for producing multivesicular liposomes involve removal of the solvent after liposome formation, whereby solvent removal by vacuum would result in destruction of the final product. Therefore, solvent removal by vacuum as disclosed in the ‘660 reference is not interchangeable with the sparging method presently claimed. Accordingly, since the ‘660 method does not employ sparging, there is no disclosure relating to gas flow rates. There simply is no suggestion of a multi-step sparging method employing different gas flow rates in the ‘660 reference. Thus, all of the cited references, including the ‘660 reference, fail to teach or suggest at least one limitation of instant claim 1, resulting in a claim that is unobvious over the prior art.

Likewise, claims 65-67, 69-72, 75-79, 84 and 89 also recite a multi-phase sparging step comprising different gas flow rates. Therefore, all of the cited references fail to teach or disclose at least one limitation of these claims, as well.

Claims 49, 65, 67, 68, 72, 74-79, 85, 86 and 89 recite specific volume fractions required for the first and second emulsions that are necessary for preparing multivesicular liposomes having a pre-determined, uniform size distribution. Claims 63, 66, 68, 74-79, 87 and 89 recite specific speeds and time parameters using impeller mixers for producing multivesicular liposomes having a pre-determined, uniform size distribution. Claims 64, 75 and 88 recite specific velocity and time parameters using static mixers for producing

multivesicular liposomes having a pre-determined, uniform size distribution. None of the cited references remotely teach or suggest these limitations, nor has the Examiner even addressed them. Applicants submit, therefore, that the present claims are novel and unobvious over the prior art, either alone or in combination.

The Examiner suggests that the claimed invention is merely “manipulation of basic method steps by an artisan to obtain the best possible results.” Applicants respectfully disagree. Applicants submit that the steps recited are not basic method steps as evidenced by the lack of art teaching or suggesting such steps even in a general manner. Failure to follow the production steps as claimed herein does not simply result in a less optimal product, but instead can result in complete inability to produce multivesicular liposomes having a pre-determined, uniform size distribution. The Examiner has failed to present prior art establishing any methods for producing multivesicular liposomes having a pre-determined, uniform size distribution. The Examiner has failed to make a *prima facie* case establishing prior art that teaches or suggests all of the limitations of the present claims. Therefore, Applicants maintain that the methods claimed herein are novel and unobvious for producing multivesicular liposomes having a pre-determined, uniform size distribution.

Rejected claims that are not specifically discussed herein are dependent upon those claims addressed in the foregoing paragraphs.


**Conclusion**

Applicants submit that the claims are now in condition for allowance. *If the Examiner does not believe the claims to be in condition for allowance, Applicants respectfully request a telephone interview be conducted with the undersigned at the number indicated below.*

No fees are believed due. Please apply any necessary charges or apply any credits to Deposit Account No. 50-3137.

Respectfully submitted,

17 January 2006

A handwritten signature in black ink, appearing to read "Diane L. Gardner", is written over a horizontal line.

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Attachments: Substitute Drawings (2 sheets, in duplicate)